Pfizer Inc
201 Tabor Road
Morris Plains, NJ 07950
Tel 973 385 2000 Fax 973 385 3761

August 23, 2002

Sandra Titus
Advisors and Consultants Staff
FDA/CDER
5630 Fishers Lane
Rockville, MD 20857

Re: September 19, 2002 meeting of the Nonprescription Drugs Advisory Committee to discuss safety issues related to the use of acetaminophen.

Dear Ms. Titus:

Pfizer Consumer Healthcare markets a variety of over-the-counter (OTC) cough/cold drug products under such popular brands as Actifed, Benadryl and Sudafed. Several of our combination cough/cold/allergy products utilize acetaminophen as the internal analgesic active ingredient. Acetaminophen is used only in combination with other active ingredients and is used in our products at total doses of between 500 and 1000 mg per dosage interval.

In response to a Food and Drug Administration initiative to review the U.S. adverse event database for acetaminophen-containing OTC drug products, Pfizer Consumer Healthcare conducted a thorough review of our U.S. adverse event database for acetaminophen-containing OTC drug products. The purpose of this review was to identify all cases of hepatic adverse events received for our U.S. acetaminophen-containing OTC drug products marketed during the period from January 1, 1994 to June 30, 2002. Our review identified 7 reports in the 8.5 year time frame.[1] The results of this review are presented in this submission and demonstrate that there is no correlation between the use of acetaminophen in our combination drug products and hepatic failure.

Pfizer Consumer Healthcare requests that this submission be included with the background materials for distribution to members of the FDA advisory committees[2] in preparation for the September 19, 2002 meeting to discuss the safety of acetaminophen. Concurrent with this submission, Pfizer Consumer Healthcare will submit this review to Docket No. 77N-0094: OTC Internal Analgesic, Antipyretic & Antirheumatic Products.

77N-0094 C240

[1] Approximately 200 million cartons of acetaminophen-containing products were sold during this interval.
[2] The Food and Drug Administration has defined these members to include members of the Nonprescription Drugs Advisory Committee, Anesthetic and Life Support Drugs Advisory Committee, Arthritis Advisory Committee, Cardiovascular and Renal Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Gastrointestinal Drugs Advisory Committee

Executive Summary:

Pfizer Consumer Healthcare reviewed the spontaneous adverse event reports for U.S. acetaminophen-containing OTC drug products for the period from January 01, 1994 to June 30, 2002. A total of seven reports of hepatic adverse events were reported in the 2,725 U.S. adverse event reports received for the acetaminophen-containing products. Of the seven reports, three were classified as serious, non-labeled, and four were classified as non-serious. All three of the serious reports were voluntarily submitted to the FDA as 15-day alerts.[3]

One of the serious reports occurred in a male with a history of regular alcohol consumption who used two acetaminophen-containing OTC drug products. A second serious report involved an intentional overdose while the third report was of a consumer who had hepatitis C and, as reported by the attending physician, was considered unrelated to product used.

Therefore, after a review of the Pfizer Consumer Healthcare U.S. spontaneous adverse event reports, no signal could be identified in the use of our acetaminophen-containing OTC drug products and hepatic events.

Background Information

Pfizer Consumer Healthcare reviewed the U.S. spontaneous adverse event reports for acetaminophen-containing OTC drug products for the period from January 01, 1994 to June 30, 2002 which were reported to Pfizer Consumer Healthcare and included in our Global Product Safety Surveillance and Information (GPSSI) adverse event database. These reports were reported to Pfizer directly.

Adverse events were categorized at the body system organ class and individual term level using the COSTART (Coding Symbols for Thesaurus of Adverse Event Terms) Thesaurus, 4th Edition. All hepatic events classified under the Digestive Body System Organ Class were reviewed.

A total of 2,725 U.S. adverse event reports for acetaminophen-containing products were included in the database for the period January 1, 1994 through June 30, 2002. Seven of the adverse event reports included terms that were categorized under the Digestive Body System Organ Class. These reports are summarized below and are listed in Table 1 (attached).

Of the seven reports:

- three were classified as serious, non-labeled and voluntarily submitted to the FDA as 15-day reports (further discussed below);

[3] The submission of the 15-day alert does not constitute an admission by the Applicant that the drug caused or contributed to the adverse event.

- four reports were non-serious;
- two were medically confirmed (both classified as serious); and
- the age range was (29-64) years of age.

The three serious adverse events reported include:

- Case 199601-0061 involved a 43-year-old male, with a history of regular alcohol consumption, who took Sinutab Maximum Strength Without Drowsiness (acetaminophen and pseudoephedrine) and Extra Strength Tylenol (acetaminophen) concurrently for several days (total dose unknown). He had fulminant hepatic failure, underwent a liver transplant and died due to complications of the transplant.

- Case 200112-0502 was a 29-year-old male who overdosed on 50-60 tablets of three Unisom® products: Unisom with Pain Relief (acetaminophen and diphenhydramine); Unisom Sleep Gels (diphenhydramine); Unisom (doxylamine) (total dose of acetaminophen is unknown). He had elevated liver enzymes, which resolved after three days.

- Case 20011-0895 was a 56-year-old female took Sinutab Sinus Maximum Strength Without Drowsiness (acetaminophen and pseudoephedrine) for reportedly over 20 years (total dose of acetaminophen is unknown). She was diagnosed with unrelated hepatitis C. No resolution has been reported for this event.

Of the four non-serious reports, three involved elevated liver enzymes.

- In the first case (199603-0271), Sinutab Maximum Strength Without Drowsiness (acetaminophen and pseudoephedrine) was used for eight years and following discontinuation of product, liver function tests returned to normal.
- In the second case (199811-0281), it was unknown if Benadryl Allergy Sinus Headache (acetaminophen, pseudoephedrine and diphenhydramine) was discontinued and the outcome is unknown.
- In the third case (200104-0715) involving Benadryl Severe Allergy and Sinus Headache (acetaminophen, pseudoephedrine and diphenhydramine), the elevated liver function tests were thought due to unrelated hepatitis A and the patient recovered.
- In the fourth case (200107-0333), a consumer using Sudafed Sinus Headache (acetaminophen and pseudoephedrine) for three weeks and had "unspecified" liver problems. He was also taking Amiodarone concurrently. The outcome is unknown.

In conclusion, and after a review of the Pfizer Consumer Healthcare U.S. spontaneous adverse event reports, no signal could be identified in the use of acetaminophen-containing OTC drug products and hepatic events. It should be emphasized that spontaneous report data

only serve as a signal of the presence of likely cases. Because of the lack of information on exposure and incomplete ascertainment of confounders and other explanatory factors on most cases, any quantitative judgment about safety and certainly any estimate of the rate of occurrence of these events in the population (i.e., incidence) must come from structured studies such as clinical trials and epidemiological studies.

Pfizer Consumer Healthcare appreciates this opportunity to submit our review of our adverse event database for acetaminophen-containing products in preparation for the September 19, 2002 meeting of the Nonprescription Drugs Advisory Committee. If you have any questions or need additional information, please contact me at (973)-385-7250.

Sincerely,

Hans Knapp

Hans Knapp
Director, Regulatory Affairs
Pfizer Consumer Healthcare

Table 1. Spontaneous U.S. Hepatic Reports For Acetaminophen Containing Products

Case #	Produc	Dose Duration	Age /Sex	Med. Confirm	Serious/ FDA Report	Past History	Con Meds	Lab Work	COSTART	Outcome
199601-0061	→ Sinutab Max Strength w/o drowsiness tab (APAP+PSE) → Extra Strength Tylenol (APAP)	UNK / several days UNK/ several days	43 M	NO	Serious/ Y 15d	Regularly drank alcoholic beverages	None specified	UNK	Hepatic Failure	Death
200112-0502	→ Unisom Sleep gels (DPH) → Unisom w/Pain Relief tab (DPH+APAP) → Unisom (doxylamine)	UNK/ Over-dose (50-60 tabs combo of 3 prod.)	29 M	YES	Serious/ Y 15d	-	Psychotropic meds not specified	→ APAP<10 (tox >150) → LDH 580 (101-218) → AST 242 → Ca 10.6 (8.7-10.5)	Liver function test abn. Back pain Intentional overdose	Resolved
20011-0895	Sinutab Sinus Max Strength w/o Drowsiness caplets (APAP, PSE)	2 caplets TID/ > 20yrs.	56 F	YES	Serious/ Y 15d	Headache	None specified	Unspecified blood test revealed HEP C	Hepatitis Arthralgia	HEP C (ongoing); Treating physician considered events unrelated to product

Table 1 (cont) Spontaneous U.S. Hepatic Reports For Acetaminophen Containing Products

Case #	Product	Dose Duration	Age /Sex	Med Confirm	Serious/ FDA Report	Past History	Con Meds	Lab Work	COSTART	Outcome
199603-0271	Sinutab Max Strength w/o Drowsiness caplets (APAP, PSE)	2-3 caplets per day/ > 8 yrs.	Adult M	NO	Non-serious/ N	Sinus Problems	None specified	UNK	Liver function test abn. Prostatic disorder	Resolved
199811-0281	Benadryl Allergy Sinus Headache (APAP, DPH, PSE)	1 caplet as needed/ UNK	64 F	NO	Non-serious/ N	-	Premarin	UNK	Liver function test abn.	UNK
200104-0715	Benadryl Severe Allergy and Sinus HA (APAP, DPH, PSE)	2 caps/ Single dose	29 F	NO	Non-serious/ N	-	Axid, Biaxin, Motrin, unspecified inhaler	→ HIDA Scan with CCK → GB w/ U/S → HEP A Reactive → Lipase 200 → Amylase 29, 768, 798 → Alkphos 379	Hepatitis Jaundice Chest Pain Abdominal Pain Sweating Dizziness Vomiting Diarrhea Nausea	Recovered
200107-0333	Sudafed Sinus Headache caplets (APAP, PSE)	½ cap BID/ 3 wks.	58 F	NO	Non-serious/ N	HTN, Enlarged prostate	Monopril, Cardizem, Amiodarone	UNK	Liver Damage	UNK

Background package for the Nonprescription Drug Advisory Committee discussion of acetaminophen to be held on September 19, 2002

Submitted by:
Hans Knapp
Pfizer Consumer Healthcare
Morris Plains, NJ
August 23, 2002

Warner-Lambert Consumer Healthcare
Pfizer Inc
201 Tabor Road
Morris Plains, NJ 07950
Tel 973 385 2000

Pfizer Consumer Healthcare

August 23, 2002

Dockets Management Branch (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 77N-0094: OTC Internal Analgesic, Antipyretic & Antirheumatic Products

To whom it may concern:

Please accept the attached correspondence containing background materials for the September 19, 2002 meeting of the Nonprescription Drugs Advisory Committee to discuss safety issues related to the use of acetaminophen. The material has been submitted to Sandra Titus, Advisors and Consultants Staff, CDER, FDA. The material is being submitted to the docket to complete the public record.

Sincerely,

Hans Knapp
Director, Regulatory Affairs
Pfizer Consumer Healthcare

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Form I.D. No. 0215

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1 From This portion can be removed for Recipient's records

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- [ ] FedEx Priority Overnight — Next business morning
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FedEx Envelope rate not available. Minimum charge: One-pound rate

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas

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- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation

5 Packaging — * Declared value limit $500

- [x] FedEx Envelope*
- [ ] FedEx Pak* — Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
- [ ] Other

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- [ ] **SATURDAY Delivery** — Available only for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
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Dangerous Goods (including Dry Ice) cannot be shipped in FedEx packaging

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7 Payment *Bill to:*

- [x] Sender — Acct. No. in Section 1 will be billed
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			Credit Card Auth

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